Cost-effectiveness Analysis of Viscosupplementation versus Conventional Supportive Therapy for Knee Osteoarthritis in Colombia

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ABSTRACT

Background: Treatment goals for knee osteoarthritis (OA) include preservation of mobility, control of pain, and delaying total knee replacement (TKR). Objective: To estimate the cost-effectiveness of viscosupplementation (hylan G-F 20) alone compared with conventional supportive therapy (CST) in the treatment of knee OA in Colombia. Methods: Microsimulation in patients with knee OA, modeling of clinical outcomes (disease progression, symptom improvement, TKR), and estimation of associated costs were performed (drugs, diagnostic tests, procedures, and hospitalizations). The probabilities for disease progression and clinical events were correlated with patients’ characteristics. Clinical outcome information was obtained from the literature. The costs were drawn from institutional databases from health maintenance organizations and the Colombian standard tariffs handbook (ISS 2001. Agreement No. 256 of 2001. Tariffs for the health promoter Social Security EPS-ISS. Social Insurance Board of Directors. December 19, 2001). Sensitivity analyses were performed for costs and transition probabilities. Results: Monte-Carlo simulation for 1000 patients with knee OA showed that viscosupplementation with hylan G-F 20 delayed the occurrence of TKR by 3 years compared with CST. Western Ontario and McMaster Universities Arthritis Index scores indicate improvement in symptoms and function with hylan G-F 20. The incremental cost-effectiveness ratio for viscosupplementation is dominant, with reduction of US $576 in treatment cost in favor of hylan G-F 20, with more cost-effectiveness per quality-adjusted life-year during the first 10 years of treatment compared with CST. Conclusions: The results of mathematical simulation indicate that in comparison to conventional support therapies, viscosupplementation with hylan G-F 20 improved disease symptoms, joint function, and quality of life, reduced direct treatment costs, delayed TKR by 3 years, and was cost-effective in Colombia. Keywords: cost-effectiveness, hylan GF-20, osteoarthritis, total knee replacement, viscosupplementation.

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Introduction

Osteoarthritis (OA) is the most common chronic joint disease of the cartilage. It is the sixth leading cause of “years of living with disability” globally and will be the fourth leading cause of disability by the year 2020 [1]. The incidence of OA increases with age [1,2]. The population affected by OA disability is expected to double by the year 2020 [3].

Treatment strategies for OA include the use of a stepped care strategy of intraarticular injections and total knee replacement (TKR) [4]. Treatment goals for knee OA include preservation of mobility, quality of life (QOL), control of pain, and slowing of disease progression, to delay TKR, which is costly and may not be medically desirable.

Viscosupplementation includes the injection of hyaluronan or hylan G-F 20, which has been shown to be safe and effective. With appropriate care, viscosupplementation provides benefits for knee function, overall health, and health-related QOL at reduced levels of cotherapy [5].

Studies confirm that hylan G-F 20 viscosupplementation is more effective than conventional treatment, at no additional cost [6], and reduces the economic burden of knee OA treatment [7]. Adding one or more courses of hylan G-F 20 therapy to the standard treatment for 3 years indicated that appropriate use could delay the need for TKRs and generate savings [8–10].

In Colombia there are no data about the benefits and costs of hylan G-F 20 therapy in patients with OA and an economic evaluation is needed. The aim of this study was to determine the cost-effectiveness of hylan G-F 20 therapy compared with conventional supportive therapy (CST) in the treatment of knee OA in Colombia.

Conflicts of interest: J.-D. Misas and A.-M. Daza are employees of Sanofi-Aventis de Colombia S.A. and receive a salary not specifically related to the development of the article.

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**Methods**

The model considered all grades of OA (Kellgren & Lawrence grades 1-4), which were stratified by ages. For the simulations, it considered a cohort of 1000 patients aged between younger than 50 years and older than 80 years. At all age groups (<50, 50–59, 60–69, 70–79, and >80 years), 59% of the patients were men and 41% were women. The age group of 70 to 79 years had the highest number of patients (357 patients). Disease severity was calculated by taking all grades of OA into consideration, and the distribution of knee OA was based on disease severity as reported in Table 1. Most of the patients (70%) were placed in grades 2 and 3 severity scale.

**Simulation Methodology**

A microsimulation of clinical outcomes (disease progression, viscosupplementation, symptom improvement, and frequency of TKR) was done focused on a hypothetical cohort of 1000 patients with knee OA and simulated, with annual regularity, their disability over time. Clinical data including the probability of disease progression were obtained from the published literature [10–12]. The use of hylan G-F 20 was compared with the use of CST. Treatment outcomes were simulated at different time horizons in the interval of 5 to 20 years.

In this model, functional disability is expressed in terms of scores obtained on the Western Ontario McMaster University Osteoarthritis Index (WOMAC) and then translated into quality-adjusted life-years (QALYs) [13]. The WOMAC score dimensions are pain, stiffness, and functional capacity on a scale ranging from 0 through 96.

Discrete-event simulation [14] was used considering patient’s ages, sex, disease progression, and initial disease severity. Discrete-event simulation allowed modeling of different characteristics of the patients (age, sex, disease progress) over time. Patients were divided proportionally into four subgroups according to the prevalence of the OA grade according to Lussier et al. [12]. Upon entry to the model, an initial WOMAC score is randomly assigned to each patient on the basis of baseline pretreatment WOMAC scores for the population. Initial scores vary from patient to patient. Annual variation depends on clinical outcome, categorized as follows: 1) symptom improvement, 2) no change in symptoms, 3) worsening of symptoms, and 4) TKR.

The annual change in WOMAC scores for patients receiving hylan G-F 20 is estimated on the basis of results of randomized controlled trials [15–18]. The available evidence suggests that the benefit obtained by viscosupplementation with hylan G-F 20 is sustained over time [10–12,15–23]; in light of this, the WOMAC scores after the first year are assigned randomly taking into account the clinical outcome for the previous years. The information about score variation is available as reported by Raman et al. [24]. In this study, the average of the percentage change of decrease in the WOMAC scores was 9.4, 25.9, and 24.5 points on a scale ranging from 0 to 96 at 6 weeks, 6 months, and 12 months, respectively. It is assumed that the change in percentage for the scores has a normal distribution, based on kurtosis and skewedness tests for the whole of the patient data. Because of the lack of available scientific evidence showing the distribution of WOMAC scores according to OA degrees, in order for the model to have an adjudication rule for assigning the degree of OA according to the compounded WOMAC score, an arbitrary classification was made for each of the dimensions in the scale, dividing the scale into four equal portions. This was done with the objective of assigning treatment costs according to OA degrees.

It was assumed that hylan G-F 20 was given once or twice a year (one 6-ml injection per application) [25]. CST included analgesics (nonsteroidal anti-inflammatory drugs and opioids), intraarticular corticosteroids, and arthroscopy for debridement and/or correction of associated injuries; physiotherapy, and recommendations of lifestyle changes (weight loss). In most cases, the common outcome for the terminal degenerative disease is surgical treatment with TKR.

Each replication was of 1000 patients. Each run is of N replications, allowing for a 95% confidence interval calculation [22]. The expected results include the average WOMAC score at the beginning and in the subsequent years and QALYs until the end of the stipulated time horizon.

The model was implemented using Microsoft Excel and Visual Basic macros, taking into account, in order to perform the dynamic simulation for the patients in the cohort, randomization of variables and the calculation of results derived from them.

The costs of the two treatments were taken from Sistema de Información de Precios de Medicamentos (SISMED) (Drug Information System of the Ministry of Social Protection) and “Farmaprecios” database. Other direct costs generated by medical services necessary to manage the disease (e.g., physical therapy) were also included. The accounting of medication costs has included drug acquisition and administration, pretreatment evaluation, routine laboratory parameters, and diagnostic imaging. These costs and TKR costs were taken mainly from Seguro Obligatorio de Accidentes de Tránsito (SOAT) tariff Manual 2012 and ISS 2001 tariffs [26].

Various conventional alternatives for support therapies for the knee OA treatment were considered in this study, and several simulations were performed to identify all the relevant costs and consequences for each one. Direct, average, and total costs, cost-effectiveness ratios, and incremental cost-effectiveness ratios (ICER) were all used to compare hylan G-F 20 viscosupplementation against CST.

Results of treatment were considered in certain horizons, but the reference case was predefined as 20 years of follow-up. During the simulation, the expected values for all economic and clinical outcomes were obtained for each patient. The summary of results across all patients in the cohort provides expected values for the group as a whole.

The cost-effectiveness ratio was expressed in terms of incremental cost per QALY gained compared with CST [27]. The analysis was made from the third-party payer perspective, the costs and effectiveness were discounted at an annual discount rate of 3%, and alternative rates were used as appropriate for sensitivity analysis. To address the uncertainty about model inputs, a first-order Monte-Carlo simulation was used. In a second-order Monte-Carlo simulation, the model was run for 100 replications, allowing calculation of the mean values and the 95% confidence intervals for clinical outcomes, cost acceptability curves, and cost-effectiveness ratio. The parameter variations were applied simultaneously in probabilistic sensitivity analysis on the basis of their respective estimated distribution, which includes 1) percentage variation in the WOMAC score to 6 months (which can be interpreted as efficacy); 2) health state utilities for the WOMAC interval; and 3) cost of health care services by the WOMAC interval as explained above. Sensitivity analyses were performed for costs and transition probabilities between degrees of knee OA.

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**Table 1 – Distribution of knee osteoarthritis based on disease severity.**

<table>
<thead>
<tr>
<th>Severity scale according to Kellgren &amp; Lawrence</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>22.4</td>
</tr>
<tr>
<td>Grade 2</td>
<td>37.4</td>
</tr>
<tr>
<td>Grade 3</td>
<td>33.5</td>
</tr>
<tr>
<td>Grade 4</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Results

Annual progression of the disease comparing the use of hylan G-F 20 alone and CST was calculated, taking into consideration the state of the symptoms (improved, unchanged, and deteriorated), as presented in Table 2. Annual disease progression comparison results indicate that 87% of the patients treated with hylan G-F 20 show improved symptoms compared with 25% of the patients treated with CST. The simulation showed that only 6.4% of group 4 patients treated with hylan G-F 20 underwent TKR while 12.8% of the patients under CST had a need for it. In patients with grade 4 OA treated with viscosupplementation using hylan G-F 20, the occurrence of TKR is delayed by 3 years, compared with patients treated with CST.

Through the simulation run, the average total cost by patient was US $27,541 for hylan G-F 20 and US $ 27,203 for CST in a 20-year time horizon. The comparison between the average costs of the two alternatives was performed as shown in Figure 1. These results have indicated that the average cost was slightly higher for CST than for hylan G-F 20 in the first years of simulation and tends to be progressively less different by the 20th year.

Economic evaluations were performed using pain, stiffness, and functional ability; QALY was the main parameter used to evaluate the economic benefit of treatment. QALY for hylan G-F 20 was 15.43 as compared with 14.34 for CST, resulting in a significant improvement of 1.09 in favor of hylan G-F 20. Viscosupplementation with hylan G-F 20 improved the patient’s QOL as compared with CST.

The cost-effectiveness plane was plotted using difference in QALY versus difference in costs as shown in Figure 2. Monte-Carlo simulations were used to generate an ICER calculated from the simulated data and repeated several times to get ICER distribution. In the scatter plot of incremental costs and QALY, most of the points were located in the right quadrants of the cost-effectiveness plane, suggesting a greater effectiveness for hylan G-F 20. Considering that hylan G-F 20 treatment is more effective and is less costly, it dominates CST, with most of the results of microsimulations falling in the quadrant that represents higher clinical benefits and lower costs.

In a 10-year follow-up simulation period, the ICER for viscosupplementation was dominant, with the following average values, respectively, for hylan G-F 20 and CST: QALY of 8.12 and 7.81 (0.31 in favor of hylan G-F 20) and treatment costs of US $14.128 and US $13.552, with a reduction of US $576 in favor of hylan G-F 20.

A cost-effectiveness scatter plot graph was obtained from the model execution, using deltas of QALYs versus deltas of costs between evaluated alternatives at 5, 10, 15, and 20 years of simulation, as shown in Figure 3. It can be perceived that to the extent that the time horizon progressed from 5 to 20 years, most of the points appeared in the quadrant at the bottom right of the graph (zone of higher effectiveness and lower cost), indicating that treatment with hylan G-F 20 tended to dominate the comparator, especially during the first 10 years of simulation.

Discussion

A pharmacoeconomic comparison between viscosupplementation using hylan G-F 20 against CST in treatment of knee OA was performed to assess differences in relevant outcomes, such as WOMAC scores and costs. Published data on disease progression and treatments indicated that more patients treated with hylan G-F 20 showed clinical improvement than did those treated with CST. The number of patients who underwent TKR was higher in the CST group than in the hylan G-F 20 group, which can be considered an important indicator of tendency for cost savings given the expensive surgical procedure [8,19]. Viscosupplementation delayed the occurrence of TKR. The initial evidence showed that hylan G-F 20 delayed TKR by an average of 2.67 years [7]. The model built here, however, has included data [10] that reported a TKR delay of 3.8 years with the use of hylan G-F 20 in Kellgren & Lawrence grade 4 osteoarthritis in 75% of the knees and combined it with the results reported as well [11]. The ability of hylan G-F 20 to delay TKR is advantageous for patients for whom TKR is not medically appropriate [10].

Comparison of WOMAC scores of function, pain, and stiffness for a time period of up to 20 years showed that viscosupplementation using hylan G-F 20 resulted in better scores for function, pain, and stiffness, indicating improvements in joint function and symptoms. Viscosupplementation improved the QOL in the present model as observed previously [22].

Cost comparisons and economic evaluations of treatments using discrete-event simulation models are helpful to inform decisions regarding resources utilization, offering flexibility to represent different stages of a disease, patient ages, sex, and disease progression [27,28]. This model followed Drummond’s methods of economic evaluation for comparison of treatment options. In the simulation, calculations of 95% confidence intervals on clinical outcomes, cost-effectiveness acceptability curves, cost-effectiveness, and sensitivity analysis were performed. The reduction of direct costs in favor of viscosupplementation compared with CST was significant in the treatment of knee OA. Comparisons of average direct costs showed that CST was slightly more expensive than hylan G-F 20 therapy.

QALY is usually the chosen parameter for the measurement of effectiveness of a treatment in cost-effectiveness evaluations, considering that this parameter merges time (in years) and QOL (in this model, provided by WOMAC scores). Knee OA, however, is not a life-threatening condition; the number of life-years lived is similar between different knee OA treatments. QOL by itself can be significantly improved by more effective treatments through reduction of pain and suffering and improvement of function. Literature shows that there is no significant difference in the values of QALYs between the compared therapies but there is a significant difference in QOL when effective therapies such as viscosupplementation are used. Achieving gain in QALYs by way of change in QOL is more difficult than when QALY changes in terms of the amount of life [29].

In the scatter plot of incremental costs and QALYs, most of the points suggested a greater effectiveness and domination of viscosupplementation over CST. If the simulation points fall

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hylan G-F 20 (% of patients)</th>
<th>Conventional support therapy (% of patients)</th>
</tr>
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<tbody>
<tr>
<td>Improved symptoms</td>
<td>87 [17]</td>
<td>33.3</td>
</tr>
<tr>
<td>Unchanged symptoms</td>
<td>9 [17]</td>
<td>33.3</td>
</tr>
<tr>
<td>Deteriorated symptoms</td>
<td>4 [17]</td>
<td>33.3</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>6.4 [17]</td>
<td>50</td>
</tr>
</tbody>
</table>

* Equal probabilities of disease progression with conventional support therapy are assumed, considering that there is no data available in the literature to allow direct comparison with hylan G-F 20.
within the northeast and southeast quadrants (more or less costly and more effective) and 95% of the joint density is in two quadrants, it involves cost savings [27]. After 10 years of simulation follow-up, the intervention was dominant for viscosupplementation. The results indicate that viscosupplementation with hylan G-F 20 was better in terms of both cost and health outcomes.

The findings in the present model show that the use of viscosupplementation with hylan G-F 20 is cost-effective (dominant) during the first 10 years of treatment and becomes less beneficial after this period and progressively until the 20th year of simulation because of the joint deterioration related to aging, disease progression, and a higher probability of a TKR after 10 years.

The simulation allows asserting that viscosupplementation is an attractive alternative for both QOL and economics in the management of patients with knee OA who have dysfunction, stiffness, and/or pain. The differences in the ratio of cost-effectiveness are mainly explained by the increased likelihood of having a knee replacement due to aging and disease progression. The SD also increases because there is variability in clinical outcomes. To the extent that the disease progresses, there are changes in associated costs showing an increasing trend.

Cost-effectiveness models of hylan G-F 20 for knee OA were developed earlier [7,20,21] using dynamic simulation techniques to estimate the impact of functional disability and economic outcomes in patients that resulted in 3-year savings [9]. Viscosupplementation had a budgetary impact that led to net savings during 10 years and reduced the economic burden of knee OA on the health system by delaying TKR [7], supporting the results presented in this article.

One of the strengths of the model is that it takes all grades of OA (Kellgren & Lawrence grades 1–4) and is stratified by ages. One of the main limitations of the present study is that most of the variables were taken from the literature using populations that may differ from the Colombian population, where epidemiological data, disease management, and progression can be different. This could change the results of the model.

The model developed for this article allowed us to assess the cost-effectiveness of hylan G-F 20 and CST therapies in Colombia. Hylan G-F 20 viscosupplementation is an attractive alternative for patients with knee OA from both the clinical perspective and the economic perspective.

Fig. 1 – Comparison of average cost between between hylan G-F 20 and conventional support therapy was done by plotting the average cost of treatment (US $) versus time in years. Solid line represents the average cost of hylan G-F 20. Dotted line represents the average cost of conventional support therapy.

Fig. 2 – The cost-effectiveness plane was plotted using the difference in QALYs versus difference in costs to look at the cost-effectiveness of hylan G-F 20 treatment over conventional support therapies. QALY, quality-adjusted life-year.
Fig. 3 – The cost-effectiveness plane was plotting using differences in QALYs versus difference in costs for 5, 10, 15, and 20 years. QALY, quality-adjusted life-year.
Conclusions

The results of a simulation using a mathematic model developed to perform a comparison of viscosupplementation with hylan G-F 20 versus CST in Colombia has shown an improvement in direct costs for the treatment of patients with knee OA. It was also shown that viscosupplementation delayed the need for TKR by 3 years compared with CST. Viscosupplementation with hylan G-F 20 is dominant, in the pharmacoeconomic context, especially during the early years.

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